IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Donoho *et al.*

Serial No.:	09/733,387	Group Art Unit:	1646
Filed:	12/07/2000	Examiner:	R. Li
For:	Novel Human Membrane Proteins and Polynucleotides Encoding the Same	Attorney Docket No.:	LEX-0104-USA

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APPEAL BRIEF

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APPEAL BRIEF

Sir:

Appellants hereby submit an original and two copies of this Appeal Brief to the Board of Patent Appeals and Interferences ("the Board") in response to the Final Office Action mailed on January 17, 2003. The Notice of Appeal was timely submitted on April 17, 2003, and was received in the Patent and Trademark Office ("the Office") on April 23, 2003. This Appeal Brief is timely submitted in light of the concurrently filed Petition for an Extension of Time of one month to and including July 23, 2003, and authorization to deduct the fee as required under 37 C.F.R. § 1.17(a)(1) from Appellants' Representatives' deposit account. The Commissioner is also authorized to charge the fee for filing this Appeal Brief ($160.00), as required under 37 C.F.R. § 1.17(c), to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

Appellants believe no fees in addition to the fee for filing the Appeal Brief and the fee for the extension of time are due in connection with this Appeal Brief. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason related to this communication, the Commissioner is authorized to charge any underpayment or credit any overpayment to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

I. REAL PARTY IN INTEREST

The real party in interest is the Assignee, Lexicon Genetics Incorporated, 8800 Technology Forest Place, The Woodlands, Texas, 77381.

II. RELATED APPEALS AND INTERFERENCES

Appellants know of no related appeals or interferences that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF THE CLAIMS

The present application was filed on December 7, 2000, claiming the benefit of U.S. Provisional Application Number 60/169,427, which was filed on December 7, 1999, and included original claims 1 -5. A Restriction and Election Requirement was issued on May 1, 2002, separating the original claims into three separate and distinct inventions. In a response to the Restriction and Election Requirement submitted to the Office on May 30, 2002, Appellants elected without traverse the claims of the Group I invention (original claims 1-3) for prosecution on the merits, amended claims 1 and 2 to further improve their clarity, and cancelled claims 4 and 5 without prejudice and without disclaimer as drawn to non-elected inventions.

A First Official Action on the merits ("the First Action") was issued on June 28, 2002, in which claims 1-3 were rejected under 35 U.S.C. § 101 as allegedly lacking a patentable utility, claims 1-3 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, claim 1 was rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement for the full scope of the claimed invention, and claim 1 was rejected under 35 U.S.C. § 112, first paragraph, as allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. In a response to the First Official Action submitted to the Office on October 28, 2002 ("Response to the First Action"), Appellants addressed the rejections of claims 1-3, and added new claims 6-9.

A Second and Final Official Action ("the Final Action") was mailed on January 17, 2003, maintaining the rejection of claims 1-3 and 6-9 under 35 U.S.C. § 101 as allegedly lacking a patentable utility, claims 1-3 and 6-9 under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, claim 1 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement for the full scope of the claimed invention, and claim 1 under 35 U.S.C. § 112, first paragraph, as allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. In a response to the Second and Final Office Action submitted on March 17, 2003 ("Response to the Final Action"), Appellants again addressed the rejections of claims 1-3 and 6-9. An

Advisory Action ("the Advisory Action") was mailed on April 17, 2003, maintaining the rejection of claims 1-3 and 6-9 under 35 U.S.C. § 101 as allegedly lacking a patentable utility, claims 1-3 and 6-9 under 35 U.S.C. § 112, first paragraph, as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, claim 1 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement for the full scope of the claimed invention, and claim 1 under 35 U.S.C. § 112, first paragraph, as allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Therefore, claims 1-3 and 6-9 are the subject of this appeal. A copy of the appealed claims are included below in the Appendix (Section IX).

IV. STATUS OF THE AMENDMENTS

As no amendments subsequent to the Final Action have been filed, Appellants believe that no outstanding amendments exist.

V. SUMMARY OF THE INVENTION

The present invention relates to Appellants' discovery and identification of novel human polynucleotide sequences that encode novel seven transmembrane protein receptor proteins, specifically G-protein coupled receptors (GPCRs) (specification at page 2, lines 7-10). GPCRs have been associated with transduction pathways involving G-proteins or PPG proteins (specification at page 2, lines 2-3).

The presently claimed polynucleotide sequences were compiled from gene trapped human cells in conjunction with cDNAs generated from human lymph node and bone marrow mRNAs (specification at page 4, lines 13-16).

The specification details a number of uses for the presently claimed polynucleotide sequences, including in assessing gene expression patterns, particularly using a high throughput "chip" format (see, for example, the specification at page 33, lines 5-26), and in determining the genomic structure (see, for example, the specification at page 11, line 5).

VI. ISSUES ON APPEAL

1. Do claims 1-3 and 6-9 lack a patentable utility?
2. Are claims 1-3 and 6-9 unusable by a skilled artisan due to a lack of patentable utility?
3. Are claims 1 and 6-9 enabled?
4. Do claims 1 and 6-9 meet the written description requirement?

VII. GROUPING OF THE CLAIMS

For the purposes of the outstanding rejections under 35 U.S.C. § 101 and 35 U.S.C. § 112, first paragraph rejection associated with utility, the claims will stand or fall together. For the purposes of the outstanding rejections under 35 U.S.C. § 112, first paragraph rejection associated with enablement and written description, claims 1 and 6-9 stand or fall together.

VIII. ARGUMENT

A. Do Claims 1-3 and 6-9 Lack a Patentable Utility?

The Final Action first rejects claims 1-3 and 6-9 under 35 U.S.C. § 101, as allegedly lacking a patentable utility due to not being supported by either a specific and substantial or a well-established utility.

First, as set forth in the response to the First Action and the response to the Final Action, Appellants would like to invite the Board's attention to the fact that a sequence sharing over 90% percent identity at the amino acid level over the entire length of the described sequence is present in the leading scientific repository for biological sequence data (GenBank), and has been annotated by third party scientists *wholly unaffiliated with Appellants* as "Homo sapiens similar to G protein-coupled receptor 56" (GenBank accession number XM_169439; alignment and GenBank report provided in **Exhibit A**). In disclosing biologically validated exon splice junctions, the claimed sequence provides physical evidence that effectively trumps the hypothetical conclusions provided by bioinformatics analysis of the corresponding genomic region conducted without supporting physical data. This can clearly be seen by examination of the alignment of the claimed sequence with XM_169439. The GenBank report for accession number XM_169439 indicates that this sequence was predicted by an automated computational

gene prediction analysis. However, Appellants' sequence is clearly the true transcript, as an extra exon that is not present in Appellants' expressed sequence is present in the XM_169439 sequence. Thus, the claimed sequence clearly meet the requirements of 35 U.S.C. § 101.

Furthermore, Appellants would like to invite the Board's attention to the fact that two expressed (as opposed to predicted) sequences sharing 100% percent identity at the protein level with the claimed sequence have been described and annotated by different third party scientists *wholly unaffiliated with Appellants* as "Homo sapiens GPR97 mRNA for G protein-coupled receptor 97" (GenBank accession number AB049169; alignment and GenBank report provided in **Exhibit B**), and "Novel G protein-coupled receptor protein and DNA thereof" (GenBank accession number BD170396; alignment and GenBank report provided in **Exhibit C**), and two additional expressed (as opposed to predicted) sequences sharing greater than 99% identity at the protein level with the claimed sequence have been described and annotated by different third party scientists *wholly unaffiliated with Appellants* as "Homo sapiens similar to G protein-coupled receptor 56 (GPR97)" (GenBank accession number NM_170776; alignment and GenBank report provided in **Exhibit D**), and "Homo sapiens G-protein coupled receptor 97 (GPR97)" (GenBank accession number AY140959; alignment and GenBank report provided in **Exhibit E**). The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. Given all of these GenBank annotations, there can be no question that those skilled in the art would clearly believe that Appellants' sequence is a G-protein coupled receptor (GPCR), specifically GPR97. Thus, the claimed sequence clearly meet the requirements of 35 U.S.C. § 101.

The Final Action questioned this assertion of utility, stating that "there is no sufficient and credible information that indicates the published sequence is a truly functional GPCR" (the Final Action at page 4). However, in both the response to the First Action and the Response to the Final Action, Appellants pointed out that a sequence sharing 68% percent identity and 78% similarity at the amino acid level over the entire length of the described sequence is present in the leading scientific repository for biological sequence data (GenBank), and has been annotated by different third party scientists *wholly unaffiliated with Appellants* as "Mus musculus Pb99 gene sequence" (GenBank accession number AF249738; alignment and GenBank

report provided in **Exhibit F**). This protein is clearly the murine homolog of the described human sequence, and has been **functionally** characterized by the same third party scientists as a G-protein coupled receptor, as evidenced by the title and text of the manuscript describing this gene (Cloning and **Functional** (emphasis added) Characterization of the Early-Lymphocyte-Specific *Pb99* Gene; Mol. Cell. Biol. *20*:4405-4410, 2000; **Exhibit G**). Thus, this argument clearly does not support the alleged lack of utility.

The Examiner has repeatedly denied that the extensive homology between Appellants' sequence and those sequences presented above confers a patentable utility to Appellants sequence, by questioning prediction of protein function based upon protein homology. In support of this allegation, the First Action cited Bork and Koonin (1998, Nature Genetics *18*:313-318; "Bork and Koonin"), Ji *et al.* (1998, J. Biol. Chem. *273*:17299-17302; "Ji") and Yan *et al.* (2000, Science *290*:523-527; "Yan"). Appellants will first set forth the shortcomings of these articles, and then point out the failure of these articles (or any such articles) to support the alleged lack of utility of the presently claimed sequence.

First, with regard to the Bork and Koonin article, Bork and Koonin themselves conclude "(i)n summary, the currently available methods for sequence analysis are sophisticated, and while further improvements will certainly ensue, they are already capable of extracting subtle but functionally relevant signals from protein sequences (Bork and Koonin, page 317). Thus, the Bork and Koonin article is hardly indicative of a high level of uncertainty in assigning function based on sequence, and thus does not support the alleged lack of utility.

With regard to Ji, an exact quote from Ji completely undermines the question of asserted utility based upon protein homology: "a substantial degree of amino acid homology is found between members of a particular subfamily, but comparisons between subfamilies show significantly less or no similarity" (Ji at 17299, first paragraph, emphasis added). This quote suggests that homology with members of a G-protein coupled receptor is indicative that the particular sequence is in fact a member of that subfamily - the fact that there is little or no homology between subfamilies is completely irrelevant. Thus, Ji does not support the alleged lack of utility.

Furthermore, regarding Yan, this paper cites only one example, two isoforms of the anhidrotic

ectodermal dysplasia (EDA) gene, where a two amino acid change conforms one isoform (EDA-A1) into the second isoform (EDA-A2). However, while it is true that this amino acid change results in binding to different receptors, it is important to note that the different receptors bound by the two isoforms are in fact related (Yan at page 523). Furthermore, the EDA-A2 receptor was correctly identified as a member of the tumor necrosis factor receptor superfamily based solely on sequence similarity (Yan at page 523). Thus, Yan does not suggest a high level of uncertainty in assigning function based on sequence, and thus also does not support the alleged lack of utility.

Thus, while Appellants have provided evidence of record that conclusively establishes that those skilled in the art would believe that the specifically claimed sequence encodes a GPCR, specifically GPR97, the Examiner has provided no evidence that directly establishes that the specifically claimed sequence does not encode a GPCR. Accordingly, the evidence of record compels a finding that the present invention has a patentable utility. Furthermore, with regard to the citation of journal articles to support an allegation of a lack of utility, the PTO has repeatedly attempted to deny the utility of nucleic acid sequences based on a small number of publications that call into doubt prediction of protein function from homology information and the usefulness of bioinformatic predictions, of which these articles are merely the latest examples. Appellants readily agree that there is not 100% consensus within the scientific community regarding prediction of protein function from homology information, and further agree that prediction of protein function from homology information is not 100% accurate. However, Appellants respectfully point out that the lack of 100% consensus on prediction of protein function from homology information is **completely irrelevant** to the question of whether the claimed nucleic acid sequence has a substantial and specific utility, and that 100% accuracy of prediction of protein function from homology information is **not the standard** for patentability under 35 U.S.C. § 101. Appellants respectfully point out that, as discussed above, the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be **believable**. Appellants submit that the overwhelming majority of those of skill in the relevant art would **believe** prediction of protein function from homology information and the usefulness of bioinformatic predictions to be powerful and useful tools, as evidenced by hundreds if not thousands of journal articles (which Appellants will submit to the Office if the Board truly

doubts Appellants' assertion that the overwhelming majority of those of skill in the art place a high value on prediction of protein function from homology information and the usefulness of bioinformatic predictions), and would thus **believe** that Appellants sequence is a GPCR. As **believability** is the standard for meeting the utility requirement of 35 U.S.C. § 101, and **not** 100% consensus or 100% accuracy, Appellants submit that the present claims must clearly meet the requirements of 35 U.S.C. § 101.

Furthermore, the **PTO itself** does not require 100% identity between proteins to establish functional homology. Example 10 of the Revised Interim Utility Guidelines Training Materials only requires a similarity score greater than 95% to establish functional homology (pages 53-55; **Exhibit H**). Thus, scientific publications that generally assert that very small changes between amino acid sequences can lead to changes in function, or publications describing specific examples of proteins, distinct from Appellants sequence, where a minor change in amino acid sequence has lead to a change in function, have been viewed by the PTO itself as irrelevant to the question of utility, and thus do not support the Examiner's allegation that the presently claimed sequence lacks utility. Therefore, the present utility rejection must fail as a matter of policy, as a matter of science, and as a matter of law.

Rather, with regard to the utility of the presently claimed sequence, as 60% of the pharmaceutical products currently being market by the entire industry target G-protein coupled receptors (Gurrath, 2001, Curr. Med. Chem. *8*:1605-1648; abstract presented in **Exhibit I**), a preponderance of the evidence clearly weighs in favor of Appellants' assertion that the skilled artisan would readily recognize that the presently described sequences have a specific (the claimed GPCR proteins are encoded by a specific locus on the human genome, see below), credible, and well-established utility, for example in tracking gene expression, as described in the specification as originally filed, at least at page 33, lines 5-26. In particular, the specification describes how the described sequences can be represented using a gene chip format to provide a high throughput analysis of the level of gene expression. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934 (**Exhibit J**), 5,556,752 (**Exhibit K**), 5,744,305 (**Exhibit L**), 5,837,832 (**Exhibit M**), 6,156,501 (**Exhibit N**) and 6,261,776 (**Exhibit O**). Evidence of the "real world" substantial utility of the present

invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies that have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, one such company (Rosetta Inpharmatics) was viewed to have such "real world" value that it was acquired by large a pharmaceutical company (Merck) for significant sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, there can be no doubt that the skilled artisan would know how to use the presently claimed sequences (see Section VIII(B), below), strongly arguing that the claimed sequences have utility. Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. As the present sequences are specific markers of the human genome (see below), and such specific markers are targets for the discovery of drugs that are associated with human disease, those of skill in the art would instantly recognize that the present nucleotide sequences would be ideal, novel candidates for assessing gene expression using such DNA chips. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequences, must in themselves be useful. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Final Action questioned this utility, stating "(s)ince the disclosure does not reveal any activity/functions of the nucleotide sequence or the protein encoded by the nucleotide sequence, one skilled in the art would not know how to use the claimed sequences" (the Final Action at page 7). However, this argument is thwarted by the fact that skilled artisans already have used and continue to use sequences such as Appellants in gene chip applications. Appellants respectfully point out that this is exactly how most gene chip applications are carried out. Expression profiling does **not** require a knowledge of the function of the particular nucleic acid on the chip - rather the gene chip indicates which DNA fragments are expressed at greater or lesser levels in two or more particular tissue types. Therefore, this argument also fails to support

the alleged lack of utility of the presently claimed compositions.

Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304; **Exhibit P**). The results have been a stunning success as the utility of human genomic data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153; **Exhibit Q**). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

Although Appellants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), Appellants noted in the Response to the First Action and the Response to the Final Action, as a further example of the utility of the presently claimed polynucleotide, as described in the specification at least at page 11, line 5, the present nucleotide sequences have a specific utility in "determining the genomic structure" of the allele encoding the presently claimed sequence. This is evidenced by the fact that SEQ ID NO:43 can be used to map 12 coding exons of the gene encoding SEQ ID NO:43 on chromosome 16 (present within a chromosome 16 clone; GenBank Accession Number AC018552; alignment and the first page from the GenBank report are presented in **Exhibit R**). Appellants respectfully remind the Board that only a minor percentage (2-4%) of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). As described above, such biologically validated

splice junctions are superior to splice junctions that may have been predicted from genomic sequence alone, and, as detailed in the specification, at least at page 11, lines 7-11, that "sequences derived from regions adjacent to the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (*e.g.*, splice acceptor and/or donor sites), *etc.*, that can be used in diagnostics and pharmacogenomics". Appellants respectfully submit that the practical scientific value of biologically validated, expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts.

Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of human chromosome 16 that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence. For further evidence in support of the Appellants' position, the Board is requested to review, for example, section 3 of Venter *et al.* (*supra*, at pp. 1317-1321, including Fig. 11 at pp.1324-1325; **Exhibit P**), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The requirement for a **specific** utility, which is the proper standard for utility under 35 U.S.C. § 101, should not be confused with the requirement for a **unique** utility, which is clearly an improper standard. The fact that other expressed sequences could be used to track gene expression patterns on a gene chip, or the fact that a small number of other nucleotide sequences could be used to map the protein coding regions in this specific region of chromosome 16, does not mean that these uses of Appellants' sequence are not specific utilities. As clearly stated by the Federal Circuit in *Carl Zeiss*

Stiftung v. Renishaw PLC, 20 USPQ2d 1101 (Fed. Cir. 1991):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

In other words, Appellants' sequence does not have to be the **only** sequence capable of providing such a utility. It is important not to confuse the requirements of a **specific** utility with a **unique** utility. If every invention were required to have a unique utility, the Patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, just to name a few particular examples, because examples of each of these have already been described and patented. However, only the briefest perusal of virtually any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions every week. Furthermore, if a composition needed to be unique to be patented, the entire class and subclass system would be an effort in futility, as the class and subclass system serves solely to group such common inventions, which would not be required if each invention needed to have a unique utility. In view of the above standards and "common sense" analysis, there can be little question that the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Furthermore, it has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974; "*Langer*"); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971). As clearly set forth in *Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

Langer at 297, emphasis in original. As set forth in the MPEP, "Office personnel must provide evidence sufficient to show that the statement of asserted utility would be considered 'false' by a person of ordinary skill in the art" (MPEP, Eighth Edition at 2100-40, emphasis added). Thus, the present claims clearly meet

the requirements of 35 U.S.C. § 101.

Regarding the utility requirements under 35 U.S.C. § 101, the Federal Circuit has clearly stated "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 185 F.3d 1364, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 149 F.3d 1368, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (U.S., 1980)). Thus, based on the relevant case law, the present claims clearly meet the requirements of 35 U.S.C. § 101.

The Final Action also questioned the applicability of this case law, stating that "the Response cites a device case law" and "(t)hus, applicants' argument citing a case law regarding a device is irrelevant to the instant case" (the Final Action at page 5). Section 101 of the Patent Act of 1952, 35 U.S.C. § 101, provides that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof," may obtain a patent on the invention or discovery. Appellants point out that 35 U.S.C. § 101 covers devices (machines) as well as compositions, and makes no distinction between the two with regard to meeting the burden of complying with 35 U.S.C. § 101. Furthermore, the case law in question (*Juicy Whip Inc. v. Orange Bang Inc.*, *supra*) cites *Brenner v. Manson*, 383 U.S. 519 (1966), which the Examiner obviously believes is not "irrelevant to the instant case", since the Examiner himself cites this exact case three times in the Final Action (see the Final Action at pages 5-7). Additionally, *Cross* and *Diamond vs. Chakrabarty*, *supra*, do not concern devices, but rather compositions. Thus, this argument completely fails to support the alleged lack of utility of the presently claimed compositions.

In *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted, emphasis added. In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Finally, While Appellants are well aware of the new Utility Guidelines set forth by the USPTO, Appellants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Appellants are unaware of any significant recent changes in either 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO. This is underscored by numerous patents that have been issued over the years that claim nucleic acid fragments that do not comply with the new Utility Guidelines. As examples of such issued U.S. Patents, the Board is invited to review U.S. Patent Nos. 5,817,479 (**Exhibit S**), 5,654,173 (**Exhibit T**), and 5,552,281 (**Exhibit U**; each of which claims short polynucleotides), and recently issued U.S. Patent No. 6,340,583 (**Exhibit V**; which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems to be requiring. Additionally, the Office has recently issued U.S. Patent 6,043,052 (**Exhibit W**), which concerns an "orphan" G-Protein coupled receptor identified based only on homology to the orphan receptor GPR25, similar to the situation with Appellants' currently claimed sequence. Importantly, this issued patent also contains no examples of the "real world" utilities seemingly required in the present case. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section VIII(B), below), Appellants submit that the present polynucleotides must also meet the requirements of 35 U.S.C. § 101. While Appellants understand that each application is examined on its own merits, Appellants are unaware of any changes to 35 U.S.C. § 101, or in the interpretation of 35 U.S.C. § 101 by the Supreme Court or the Federal Circuit, since the issuance of these patents that render the subject matter claimed in these patents, which is similar to the subject matter in question in the present application, as suddenly non-statutory or failing to meet the requirements of 35 U.S.C. § 101. Thus, holding Appellants to a different standard of utility would be arbitrary and capricious, and, like other clear violations of due process, cannot stand.

For each of the foregoing reasons, Appellants submit that the rejection of claims 1-3 and 6-9 under

35 U.S.C. § 101 must be overruled.

B. Are Claims 1-3 and 6-9 Unusable Due to a Lack of Patentable Utility?

The Final Action next rejects claims 1-3 and 6-9 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by either a clear asserted utility or a well-established utility.

The arguments detailed above in Section VIII(A) concerning the utility of the presently claimed sequences are incorporated herein by reference. As the Federal Circuit and its predecessor have determined that the utility requirement of Section 101 and the how to use requirement of Section 112, first paragraph, have the same basis, specifically the disclosure of a credible utility (*In re Brana, supra*; *In re Jolles*, 628 F.2d 1322, 1326 n.11, 206 USPQ 885, 889 n.11 (CCPA 1980); *In re Fouche*, 439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971)), Appellants submit that as claims 1-3 and 6-9 have been shown to have "a specific, substantial, and credible utility", as detailed in Section VIII(A) above, the present rejection of claims 1-3 and 6-9 under 35 U.S.C. § 112, first paragraph, cannot stand.

Appellants therefore submit that the rejection of claims 1-3 and 6-9 under 35 U.S.C. § 112, first paragraph, must be overruled.

C. Are Claims 1 and 6-9 Enabled?

The Final Action next rejected claims 1 and 6-9 under 35 U.S.C. § 112, first paragraph, as allegedly not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention.

The Final Action stated that claim 1 is not enabled because "(i) there is no evidence that 22 residues are sufficient to retain the functions of the full length (*sic*) and (ii) even if so, there is no guidance regarding which 22 residues are sufficient" (the Final Action at page 10). Appellants point out that the above comment is **completely irrelevant** to determining whether the claimed compositions meet the legal requirements for patentability under 35 U.S.C. § 112, first paragraph. There is absolutely **no** requirement that all species of an invention must have all of the exact same properties. It is well established that the

enablement requirement is met if **any** use of the invention (or in this case, certain species of the invention) is provided (*In re Nelson*, 126 USPQ 242 (CCPA 1960); *Cross v. Iizuka, supra*). The Final Action also cited Wallace *et al.* (1987, Methods Enzymol. 152:432-443) for the proposition that "determining the specificity of hybridization is empirical by nature" (the Final Action at page 11). While the relevance of a 13 year old reference to the state of the art at the time of filing of the present application is questionable at best, this argument is again **completely** misplaced, because numerous uses of the claimed sequences do not require knowledge of any hybridization conditions.

Appellants point out that significant commercial exploitation of nucleic acid sequences requires no more information than the nucleic acid sequence itself. Applications ranging from gene expression analysis or profiling (utilizing, for example, arrays of short, overlapping or non-overlapping, oligonucleotides and DNA chips, as described in Section VIII(A), above) to chromosomal mapping (utilizing, for example, short oligonucleotide probes or full length DNA sequences, as described in Section VIII(A), above) are practiced utilizing nucleic acid sequences and techniques that are well-known to those of skill in the art. The widespread commercial exploitation of nucleic acid sequence information points to the level of skill in the art, and the enablement provided by disclosures such as the present specification, which include specific nucleic acid sequences and guidance regarding the various uses of such sequences. Thus, the skilled artisan can clearly make and use the claimed polynucleotides, which is **all that is required** to meet the enablement requirement under 35 U.S.C. § 112, first paragraph.

The Action questions the teaching and guidance in the specification for certain aspects of the present invention. However, as discussed above, this requirement is completely misplaced. There is sufficient knowledge and technical skill in the art for a skilled artisan to be able to make and use the claimed DNA species in a number of different aspects of the invention entirely without further details in a patent specification. For example, it is not unreasonable to expect a Ph.D. level molecular biologist to be able to use the disclosed sequence to design oligonucleotide probes and primers and use them in, for example, PCR based screening and detection methods to obtain the described sequences and/or determine tissue expression patterns. Nevertheless, the present specification provides highly detailed descriptions of techniques that can be used to accomplish many different aspects of the claimed invention, including

recombinant expression, site-specific mutagenesis, *in situ* hybridization, and large scale nucleic acid screening techniques, and properly incorporates by reference a montage of standard texts into the specification, such as Sambrook *et al.* (*Molecular Cloning, A Laboratory Manual*) and Ausubel *et al.* (*Current Protocols in Molecular Biology*) to provide even further guidance to the skilled artisan. Incorporation of material into the specification by reference is proper. *Ex parte Schwarze*, 151 USPQ 426 (PTO Bd. App. 1966). The § 112, first paragraph rejection is thus *prima facie* improper:

> As a matter of patent office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Marzocchi, supra at 369, emphasis as in original. In any event, an alleged lack of express teaching is insufficient to support a first paragraph rejection where one of skill in the art would know how to perform techniques required to perform at least one aspect of the invention. As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands, supra.* In fact, it is preferable that what is well known in the art be omitted from the disclosure. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). As standard molecular biological techniques are routine in the art, such protocols do not need to described in detail in the specification.

The Action seems to contend that the specification provides insufficient guidance regarding the biological function or activity of certain of the claimed compositions. However, such an enablement standard conflicts with established patent law. As discussed *In re Brana* (*supra*; "*Brana*"), the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Examiner cited *In re Wands* (*supra*; "*Wands*") for the proposition that the present invention could not be practiced without "undue experimentation". However, it is important to remember that in assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin, supra.* In *Wands*, the P.T.O. took the position that the applicant failed to demonstrate that the disclosed biological

processes of immunization and antibody selection could reproducibly result in a useful biological product (antibodies from hybridomas) within the scope of the claims. In its decision overturning the P.T.O.'s rejection, the Federal Circuit found that Wands' demonstration of success in four out of nine cell lines screened was sufficient to support a conclusion of enablement. The court emphasized that the need for some experimentation requiring, *e.g.*, production of the biological material followed by routine screening, was not a basis for a finding of non-enablement, stating:

> Disclosure in application for the immunoassay method patent does not fail to meet enablement requirement of 35 USC 112 by requiring 'undue experimentation,' even though production of monoclonal antibodies necessary to practice invention first requires production and screening of numerous antibody producing cells or 'hybridomas,' since practitioners of art are prepared to screen negative hybridomas in order to find those that produce desired antibodies, since in monoclonal antibody art one 'experiment' is not simply screening of one hybridoma but rather is entire attempt to make desired antibody, and since record indicates that amount of effort needed to obtain desired antibodies is not excessive, in view of Applicants' success in each attempt to produce antibody that satisfied all claim limitations.

Wands at 1400. Thus, the need for some experimentation does not render the claimed invention unpatentable under 35 U.S.C. § 112, first paragraph. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., supra.*

Furthermore, a specification "need describe the invention only in such detail as to enable a person skilled in the most relevant art to make and use it." *In re Naquin*, 158 USPQ 317, 319 (CCPA 1968); emphasis added. The present claims are thus enabled as they are supported by a specification that provides sufficient description to enable the skilled person to make and use the invention as claimed. Appellants stress that enablement must be analyzed, not in a vacuum, but "as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." *In re Moore*, 169 USPQ 236, 238 (CCPA 1971).

As set forth by the Federal Circuit, "[T]he enablement requirement is met if the description enables any mode of making and using the invention." *Johns Hopkins Univ. v. CellPro, Inc.*, 47 USPQ2d 1705, 1719 (Fed. Cir. 1998), citing *Engel Indus., Inc. v. Lockformer Co.*, 20 USPQ2d 1300, 1304 (Fed. Cir.

1991). As described in detail above, the specification details numerous applications in which claimed nucleotide sequences can be used, for example, to track gene expression using gene chips. Further, since public domain nucleotide sequences that have not been associated with any particular biological function, let alone validated as coding sequences, are used every day in gene chip applications, it defies logic that undue experimentation would be required to use the presently described nucleotide sequences, which have been biologically validated as coding sequences, in the very same gene chip applications.

Appellants therefore submit that the rejection of claims 1 and 6-9 under 35 U.S.C. § 112, first paragraph, must be overruled.

D. Do Claims 1 and 6-9 Lack Sufficient Written Description?

The Final Action next rejected claims 1 and 6-9 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Final Action stated that claim 1 fails to meet the written description requirement because it "does not require that the nucleic acid molecules possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature" (the Final Action at page 11). However, the Final Action **admitted** that claim 1 in fact does include a distinguishing feature, specifically, that the nucleic acid molecule must include "a stretch of at least 22 consecutive nucleotides of [S]EQ ID NO:43 (the Final Action at page 11; error corrected). Appellants respectfully point out that this is **all that is required** of claim 1 to meet the written description requirement of 35 U.S.C. § 112, first paragraph.

In the Advisory Action, the Examiner states that "(a) stretch of at least 22 consecutive nucleotides of SEQ ID NO:43 is not a conserved structure and a distinguishing feature, because such a limitation does not require that the nucleic acid molecules possess any particular biological activity, nor specify at least which 22 consecutive nucleotides of SEQ ID NO:43 and how the stech (*sic*) of nucleotides is related to their biological functions" (the Advisory Action at page 3). Appellants point out that **every aspect** of this argument fails to take into consideration the proper basis for compliance with the written description

requirement under 35 U.S.C. § 112, first paragraph. First, the Examiner seems to be requiring that the structural limitation of "at least 22 consecutive nucleotides of SEQ ID NO:43" have a functional basis, specifically that it possess a "particular biological activity". This argument completely defies logic - of course this **structural** limitation does not have a functional basis. Second, the limitation of "at least 22 consecutive nucleotides of SEQ ID NO:43" does in fact have a particular conserved structure, specifically, each and every species is conserved within the nucleotide sequence of SEQ ID NO:43. Finally, the Examiner's allegation that the limitation "at least 22 consecutive nucleotides of SEQ ID NO:43" does not include a distinguishing feature directly contradicts the fact that the Examiner has admitted that this limitation is completely free of the prior art. Thus, these species are each unique markers of the nucleotide sequence of SEQ ID NO:43. Thus, the Examiner's argument in no way supports the allegation that claim 1 does not meet the written description requirement under 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 112, first paragraph, requires that the specification contain a written description of the invention. The Federal Circuit in *Vas-Cath Inc. v. Mahurkar* (19 USPQ2d 1111 (Fed. Cir. 1991); "*Vas-Cath*") held that an "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.*" *Vas-Cath*, at 1117, emphasis in original. However, it is important to note that the above finding uses the terms reasonable clarity to those skilled in the art. Further, the Federal Circuit in *In re Gosteli* (10 USPQ2d 1614 (Fed. Cir. 1989); "*Gosteli*") held:

> Although [the applicant] does not have to describe exactly the subject matter claimed, . . . the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.

Gosteli at 1618, emphasis added. Additionally, *Utter v. Hiraga* (6 USPQ2d 1709 (Fed. Cir. 1988); "*Utter*"), held "(a) specification may, within the meaning of 35 U.S.C. § 112 ¶1, contain a written description of a broadly claimed invention without describing all species that claim encompasses" (*Utter*, at 1714). Therefore, all Appellants must do to comply with 35 U.S.C. § 112, first paragraph, is to convey the invention with reasonable clarity to the skilled artisan.

Further, the Federal Circuit has held that an adequate description of a chemical genus "requires a precise definition, such as by structure, formula, chemical name or physical properties" sufficient to distinguish the genus from other materials. *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993;

"*Fiers*"). *Fiers* goes on to hold that the "application satisfies the written description requirement since it sets forth the . . . nucleotide sequence" (*Fiers* at 1607). In other words, provision of a structure and formula - the nucleotide sequence - renders the application in compliance with 35 U.S.C. § 112, first paragraph.

More recently, the standard for complying with the written description requirement in claims involving chemical materials has been explicitly set forth by the Federal Circuit:

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. *Regents of Univ. of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Thus, a claim describing a genus of nucleic acids by structure, formula, chemical name or physical properties sufficient to allow one of ordinary skill in the art to distinguish the genus from other materials meets the written description requirement of 35 U.S.C. § 112, first paragraph. As further elaborated by the Federal Circuit in *Regents of Univ. of California v. Eli Lilly and Co.*:

> In claims to genetic material ... a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA', without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art cannot, as one can do with a fully described genus, visualize or recognize the identity of members of the genus. (Emphasis added)

Thus, as opposed to the situation set forth in *Regents of Univ. of California v. Eli Lilly and Co.* and *Fiers*, the nucleic acid sequences of the present invention are not distinguished on the basis of function, or a method of isolation, but in fact are distinguished by structural features - a chemical formula, *i.e.*, the *sequence itself.*

Using the nucleic acid sequences of the present invention (as set forth in the Sequence Listing), the skilled artisan would readily be able to **distinguish** the claimed nucleic acids from other materials on the basis of the specific **structural** description provided. Polynucleotides comprising at least 22 contiguous bases from SEQ ID NO:43 are within the genus of the instant claims, while those that lack this structural

feature lie outside the genus. The claimed genus of polynucleotides is clearly defined in structural terms, which is **all that is required** of claims 1 and 6-9 to meet the written description requirement of 35 U.S.C. § 112, first paragraph.

For each of the foregoing reasons, Appellants submit that the rejection of claims 1 and 6-9 under 35 U.S.C. § 112, first paragraph, must be overruled.

IX. APPENDIX

The claims involved in this appeal are as follows:

1. (Amended) An isolated nucleic acid molecule comprising at least 22 contiguous bases of nucleotide sequence from SEQ ID NO:43.

2. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO:44; and

(b) hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO:43 or the complement thereof.

3. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:44.

6. A recombinant expression vector comprising the isolated nucleic acid molecule of claim 1.

7. The recombinant expression vector of claim 6, wherein the isolated nucleic acid molecule encodes the amino acid sequence shown in SEQ ID NO:44.

8. The recombinant expression vector of claim 7, wherein the isolated nucleic acid molecule comprises the nucleotide sequence of SEQ ID NO:43.

9. A host cell comprising the recombinant expression vector of claim 6.

X. CONCLUSION

Appellants respectfully submit that, in light of the foregoing arguments, the Final Action's conclusion that claims 1-3 and 6-9 lack a patentable utility and are unusable by the skilled artisan due to a lack of patentable utility is unwarranted. It is therefore requested that the Board overturn the Final Action's rejections.

Respectfully submitted,

July 23, 2003
Date

David W. Hibler
Agent For Appellants

Reg. No. 41,071

LEXICON GENETICS INCORPORATED
8800 Technology Forest Place
The Woodlands, TX 77381
(281) 863-3399

TABLE OF AUTHORITIES

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